REMARKS

Status of Claims

Claims 80-83 and 87-90 are currently pending. Claims 80-83 are currently amended and claims 87-90 are added. Support for the amended and added claims is found throughout the specification as originally filed, *inter alia*, in the following: page 23, lines 5-9; page 31, lines 25-28; and Example 7 and 8. Accordingly, Applicants submit that no new matter is introduced into the specification by way of the present amendments pursuant to 35 U.S.C. § 132. Applicants respectfully request entry of the amendments, reconsideration of the rejections, and allowance of the pending claims.

Claims 1-79, 84-85 and 86 have been canceled for the sole purposes of advancing prosecution and are cancelled without prejudice or disclaimer as to the claimed subject matter. Applicants reserve the right to pursue cancelled subject matter in one or more divisional or continuation applications.

Information Disclosure Statement

Applicants thank the Examiner for the consideration of the IDS papers submitted November 29, 2004, June 17, 2005, and September 11, 2006. The IDS paper indicated in the Office Action as IDS paper submitted February 20, 2001 is a copy of the IDS submitted in parent application 09/662,183 and was submitted in the present application on March 23, 2004. Per the Examiner's requests, Applicants submit a clean IDS paper listing all the reference citations submitted in the present application on March 23, 2004. Timely consideration of these references is respectfully requested.

Clam Objections

Claims 81 and 82 are objected to for the recitation of non-elected subject matter. Applicants have amended claims 81 and 82 to recite the elected sequence of SEQ ID NO: 12. Accordingly, Applicant respectfully requests withdrawal of the claim objection.

Compliance with the Sequence Rules

The Office Action sets forth an objection to the specification for failing to comply with the sequence requirements of 37 C.F.R. §§ 1.821-1.825. Applicants have amended the specification and sequence listing in accordance with these sequence rules and therefore respectfully request withdrawal of this objection.

With respect to the figures, submitted herewith are replacement drawings that amend Figures 14 and 15 to remove reference to sequence data deemed unnecessary to the understanding of the invention. Applicants believe that amendments to Figures 14 and 15 addresses the issue of sequence compliance and is sufficient to bring the application into compliance with the sequence rules.

Reply to Claim Rejections Under 35 U.S.C. § 112, first ¶

Claims 80-85 are rejected under 35 U.S.C. § 112, first ¶, because the specification, while being enabled for a method of treating photoreceptor loss in the retina of patents afflicted with macular degeneration, retinitis pigmentosa, or glaucoma, comprising administering to the eye of the patient a cell line expressing a Neublastin polypeptide comprising the amino acid sequence of SEQ ID NO: 9, 10, 11, or 12, allegedly does not reasonably provide enablement for a method of prevention as broadly claimed or a method of treating any disorder of the eye comprising administering a cell line expressing a Neublastin polypeptide, which comprises an amino acid sequence of at least 90% or at least 95% sequence identity with SEQ ID NO: 12.

Applicants respectfully disagree with this rejection. Nonetheless, applicants have amended the claims to recite a method of treating a disorder of the eye wherein the disorder is macular degeneration, retinitis pigmentosa, or glaucoma. Further, the claims have been amended to remove reference to a method of prevention. As the Examiner has already indicated that the specification is enabled for the treatment of these recited diseases, withdrawal of this rejection and an early indication of allowance is respectfully requested.

With respect to the recitation of a Neublastin polypeptide comprising an amino acid sequence of at least 90% or at least 95% sequence identity with SEQ ID NO: 12, the Examiner at page 8 of the Office Action alleges that: "The claims are overly braod in the recitation of 'at least 90% or at least 95% homology' since insufficient guidance is provided as to which of the myriad of amino acid species encompassed by the claims will retain the characteristics of being neurotrophic agents." Applicants respectfully disagree with this assessment. First, as indicated in the Office Action at page 7, the specification provides for multiple assays that may be used by one of skill in the art to assess whether a an amino acid sequence at least 90% or at least 95% homologous to SEQ ID NO: 12 would possess neurotrophic activity. Second, the analysis set forth in the Office Action appears only to consider those amino acid sequences that were elected in the present application. The specification sets forth several protein sequences that share an varying degree of homology with SEQ ID NO: 12. For example, SEQ ID NO: 16 shares 88.5% identity in 113 residues overlap; SEQ ID NO: 2 shares 91.1% identity in 112 residues overlap with SEQ ID NO: 12; and SEQ ID NO: 4 shares 97.3% identity in 113 residues overlap. These alignments were executed using the SIM - Alignment Tool for protein sequences available at http://expasy.org/tools/sim-prot.html and are provided below for the convenience of the Examiner.

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Results of SIM with:
Sequence 1: SeqIDNO:12, (113 residues)
Sequence 2: SeqIDNO:2, (200 residues)
using the parameters:
Comparison matrix: BLOSUM62
Number of alignments computed: 20
Gap open penalty: 12
Gap extension penalty: 4

91.1% identity in 112 residues overlap; Score: 531.0; Gap frequency: 0.9%

SeqIDNO:12      2 GGPGSRARAAGARGCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLSLASL
SeqIDNO:2,     90 GGRAARSGSGGA-GCRLRSQLVPVRALGLGHRSDELVRFRFCTGSCPRARSPHDLSLASL
                  **   *    ** ***************************** *** *************

SeqIDNO:12     62 LGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG
SeqIDNO:2,    149 LGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG
                  ********************************************************


Results of SIM with:
Sequence 1: SeqIDNO:12, (113 residues)
Sequence 2: SeqIDNO:4, (237 residues)
using the parameters:
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Comparison matrix: BLOSUM62
Number of alignments computed: 20
Gap open penalty: 12
Gap extension penalty: 4

97.3% identity in 113 residues overlap; Score: 588.0; Gap frequency: 0.0%

SeqIDNO:12      1 AGGPGSRARAAGARGCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLSLAS
SeqIDNO:4,    125 AGGPGNRARAAGARGCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLSLAS
                  ***** ************************************************

SeqIDNO:12     61 LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG
SeqIDNO:4,    185 LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSANPCGCLG
                  ********************************************  *****

Results of SIM with:
Sequence 1: SeqIDNO:12, (113 residues)
Sequence 2: SeqIDNO:16, (224 residues)
using the parameters:
Comparison matrix: BLOSUM62
Number of alignments computed: 20
Gap open penalty: 12
Gap extension penalty: 4

88.5% identity in 113 residues overlap; Score: 528.0; Gap frequency: 0.0%

SeqIDNO:12      1 AGGPGSRARAAGARGCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLSLAS
SeqIDNO:16    112 AGTRSSRARTTDARGCRLRSQLVPVSALGLGHSSDELIRFRFCSGSCRRARSQHDLSLAS
                  **   ****   ************ ****** **** ************** *******

SeqIDNO:12     61 LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG
SeqIDNO:16    172 LLGAGALRSPPGSRPISQPCCRPTRYEAVSFMDVNSTWRTVDHLSATACGCLG
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Further, Applicants respectfully submit that the Examiner has not set forth any evidence to support the conclusion that the Neublastin polypeptide sequence of at least 2, 4, 5, 6, 7, 9, 10, 11, 12 and 16 would not possess neurotrophic activity. In order to establish a *prima facie* case of non-enablement, the Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure. See In re Wright, 999 F.2d 1557, 1561-562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). A disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, *unless* there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. See In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, it is incumbent upon the Patent

Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

The threshold step in resolving this issue is to determine whether the Examiner has met his burden of proof by advancing acceptable reasoning inconsistent with enablement. In re Morehouse, 545 F.2d 162, 165, 192 USPQ 29, 32 (CCPA 1976). Further, even a broad allegation that the disclosure is speculative, coupled with a recitation of various difficulties which might be encountered in practice, is not sufficient basis for requiring proof of operability. In re Chilowsky, 229 F.2d 457, 462, 108 USPQ 321, 325 (CCPA 1956). In the present case, Applicants respectfully submit that the Examiner has not provided acceptable evidence that the claimed invention is inconsistent with enablement. At best, the Examiner has made broad allegations that the disclosure is speculative and recited various difficulties which might be encountered in practice of the invention. This is not a sufficient evidentiary basis for requiring proof of enablement and a shifting of the burden of proof to appellant.

In this regard, the following passage from PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996) is instructive here.

> In unpredictable art areas, this court has refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make and use other potential embodiments across the full scope of the claim. See, e.g., In re Goodman, 11 F.3d 1046, 1050-52, 29 USPQ2d 2010, 2013-15 (Fed. Cir. 1993); Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1212-14, 18 USPQ2d 1016, 1026-28 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991); In re Vaeck, 947 F.2d at 496, 20 USPQ2d at 1445. Enablement is lacking in those cases, the court has explained, because the undescribed embodiments cannot be made, based on the disclosure in the specification, without undue experimentation. But the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must

not be unduly extensive." Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). The Patent and Trademark Office Board of Appeals summarized the point well when it stated:

> The test is not merely quantitative, since a *considerable amount of experimentation is permissible*, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. Ex parte Jackson, 217 USPQ 804, 807 (1982).

In the present case, even if a considerable amount of experimentation is required to determine those Neublastin polypeptides that possess neurotrophic activity, such experimentation is routine to those of ordinary skill in the relevant art.

Moreover, applicants respectfully submit that the entire scope of claimed subject matter also meets the written description requirement of 35 U.S.C. 112, ¶ 1. Example 14 of the Written Description Guidelines provides useful guidance in determining what scope of claims would be allowable with respect to the written description requirement. Example 14 considers the following hypothetical claim:

> A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A → B.

The example explains that the procedures for making variants (*e.g.*, substitutions, deletions, insertions, and additions) of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Furthermore, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art. In addition, there is an actual reduction to practice of SEQ ID NO: 3, and the specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to SEQ ID NO: 3. Specifically, the PTO concludes that the hypothetical claim provides adequate written description for the following reasons:

> There is actual reduction to practice of the single disclosed species [SEQ ID NO: 3]. The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

Thus, Example 14 of the Guidelines teaches that the requirement for written description is satisfied where all variants are structurally similar to a particular sequence and there is an assay that identifies all of these structurally similar variants that are capable of the specified activity of the particular description.

Applicants respectfully submit that the scope of the claims include homologues that are structurally similar to SEQ ID NO: 12, which do not have substantial variation since all of the Neublastin polypeptides must possess a specified activity, *i.e.*, neurotrophic activity. The specification provides multiple examples of these additional embodiments and teaches an assay that would identify all of these structurally similar Neublastin polypeptides (*e.g.*, Examples 1-3), as is indicated in Office Action at page 7.

Accordingly, applicants respectfully submit that the claims raise no issue written description.

Reply to Claim Rejections Under 35 U.S.C. § 112, second ¶

Claim 80-85 are rejected under 35 U.S.C 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully submit that the present amendments to the above claims address the issues raised by the Examiner with respect to claim form. Accordingly, Applicants respectfully request withdrawal of these rejections.

Reply to Claim Rejections Under 35 U.S.C. § 102(b) in view of Algvere et al.

Claims 80-85 are rejected under 35 U.S.C. § 102(b) as being anticipated by Algvere *et al.* (Graefe's Arch Clin Exp Ophthalmol. March 1997; 235: 149-158). Applicants respectfully disagree with this rejection as Algvere *et al.* fails to teach every element of the claims.

Specifically, the Office Action states that the human Retinal Pigment Epithelial (RPE) cells disclosed by Algvere *et al.* would inherently express the recited Neublastin polypeptide. Anticipation by inherency requires that the prior art reference disclose each and every limitation of the claim.[1] Applicants respectfully submit that Algvere *et al.* fail to disclose that RPE cells inherently express the recited Neublastin polypeptide at all. The Examiner has failed to provide sufficient evidence that the RPE cells ***necessarily*** express the recited Neublastin polypeptides. Indeed, to show that RPE cells express the recited Neublastin polypeptides, the Examiner cites to pages 44 and 46 of the specification where it is taught that Neublastin is expressed in a variety of neuronal type cells. As the figure[2] below illustrates, retinal pigmented epithelial cells are a distinct cell type and separate from the neural layer of the retina. Thus, the specification does not imply that a Neublastin is expressed in the types of cells disclosed in Algvere *et al.*

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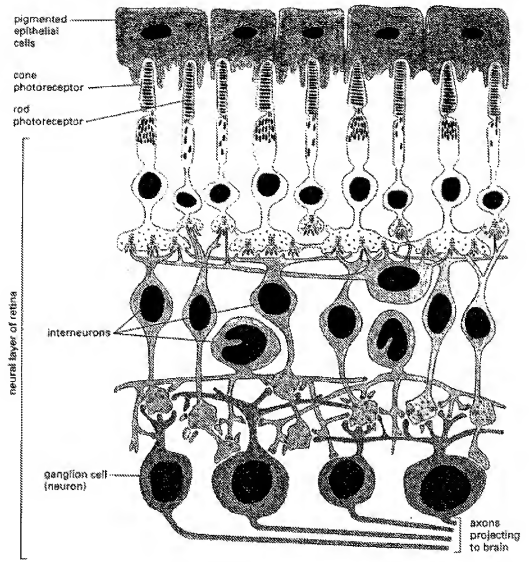
[1] *See Standard Havens Prods., v Gencor Indus., Inc.,* 953 F.2d 1360, 1369 (Fed. Cir. 1991).

[2] Alberts *et al.*, Molecular Biology of the Cell, Third Ed., Garland Publishing, Inc., New York (1994).



Nonetheless, the claims have been amended to recite a cell line wherein is genetically manipulated to express the Neublastin polypeptide. Algvere *et al.* discloses the use of primary cells (See Algvere *et al.* at page 150, right column), which are not genetically manipulated to express the Neublastin polypeptide. Accordingly, Applicant respectfully submit that Algvere *et al.* fails teach every element of the claim. Withdrawal of this rejection is respectfully requested.

Reply to Claim Rejections Under 35 U.S.C. § 102(e) in view of Greenwood et al.

Claims 80-85 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Greenwood *et al.* (U.S. Patent Publication No. 2003/0059868). Greenwood *et al.* was published from U.S. Application No. 09/559,707 filed April 27, 2000, which is not before the effective filing date of the present application. Thus, in making this rejection, the Examiner relies on the priority documents of Greenwood *et al.* application, U.S. Application Nos. 08/973,553 and 09/182,516, filed January 22, 1998 and October 30, 1998, respectively. Theses priority documents, however, do not disclose a Neublastin polypeptide. Indeed, these documents make no mention of a Neublasin polypeptide. Greenwood *et al.* therefore can not be relied upon as prior art under 35 U.S.C. § 102. Accordingly, applicants respectfully request withdrawal of this rejection.

Reply to Claim Rejections Under 35 U.S.C. § 102(e) in view of Tao et al.

Claims 80-85 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Tao *et al.* (U.S. Patent No. 6,361,771). Tao *et al.* issued from U.S. Application No. 09/543,119 filed April 5, 2000, which is not before the effective filing date of the present application. Thus, in making this rejection, the Examiner relies on the disclosure in U.S. Provisional Application No. 60/127,926, filed Apr. 6, 1999, from which U.S. Patent No. 6,361,771 claims the benefit of priority. This priority document, however, was filed after the priority documents of the present application, and therefore, does not qualify as prior art under 35 U.S.C. § 102. Further, this priority document does not disclose a Neublastin polypeptide. Indeed, the disclosure in U.S. 60/127,926 makes no mention of a Neublastin polypeptide. Thus, the first disclosure of a Neublastin polypeptide in the Tao *et al.* family is in U.S. Application No. 09/543,119, which was filed after the present application. Tao *et al.* therefore can not be relied upon as prior art under 35 U.S.C. § 102. Accordingly, applicants respectfully request withdrawal of this rejection.

Priority

The Examiner has assigned an effective filing date of July 2, 1999 for the present application. In reaching this conclusion, the Examiner alleges that the U.S. Provisional Application Nos. 60/092,229 (filed 7/9/1998), 60/097,774 (filed 8/25/1998), and 60/103,908 (filed 10/13/1998) do not enable the present invention. This issue is rendered moot as valid prior art reference under 102 with an intervening date is cited in the Office Action. But even if the Examiner was to present such a reference, applicants respectfully submit that the specifications of the priority documents fully enable the claims. Each of these documents disclose methods of treating neurodegenerative disorders. As presented above, the present claims are directed to methods of treating neurodegenerative disorders of the eye. One of skill in the art would have been able to rely on the teachings of the specifications to practice the claimed invention. Accordingly, applicants respectfully submit that the priority documents provide adequate support for the present claims.

CONCLUSION

An indication of allowance of all claims is respectfully solicited. Early notification of a favorable consideration is respectfully requested. In the event any issues remain, Applicant would appreciate the courtesy of a telephone call to their counsel to resolve such issues and place all claims in condition for allowance.

It is believed that no additional fees are required with this submission. However, in the event that additional fees are deemed necessary, or in the event of any variance between the amount enclosed and the fees determined by the USPTO, please charge or credit any such variance to the undersigned's Deposit Account No. 50-0311, Reference No. 19313-001 CON.

Respectfully submitted,

Dated: June 27, 2007 By: /Sheridan Snedden/

Ivor R. Elrifi, Reg. No. 39,529
Sheridan K. Snedden, Reg. No. 55,998
Attorney/Agent for Applicants
c/o MINTZ, LEVIN
Tel: (617) 542-6000
Fax: (617) 542-2241
Customer No. 30623

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